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Model-based study of the effects of the hemodialysis technique on the compensatory response to hypovolemia

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Background. Hemodialysis technique (dialysate composition, filter, convection/diffusion ratio, etc.) can have an impact on the patient's tendency to acute hypotension. We have examined the hypothesis that the dialysis technique affects the hypotension risk by altering the cardiovascular compensatory response to hemodialysis-induced hypovolemia.

Methods. Twelve hypotension-prone subjects were studied during six sessions of conventional bicarbonate dialysis (BD) and six sessions of acetate-free biofiltration (AFB). Blood volume (BV) control system was used in AFB to provide a BV change equivalent to the BV change observed in BD. The efficacy of reflex compensatory mechanisms was assessed by a model-based computer analysis of the BD and AFB sessions.

Results. BD sessions were complicated by hypotension more frequently than the AFB ones (34/66 BD vs. 18/66 AFB). Hypotension arose about 60 minutes earlier in BD (123 ± 41 minutes in BD vs. 183 ± 25 minutes in AFB, $P < 0.01$), and after a smaller BV reduction (hypotension BV $7.9\% \pm 2.0\%$ in BD vs. $10.9\% \pm 2.6\%$ in AFB, $P < 0.05$). Model-based computer analysis of the sessions without hypotension revealed differences in peripheral resistance adaptation ($9\% \pm 9\%$ BD vs. $19\% \pm 7\%$ AFB, $P < 0.05$) as well as in the stroke volume reduction ($19\% \pm 8\%$ BD vs. $10\% \pm 8\%$ AFB, $P < 0.001$). Model analysis of sessions with hypotension indicated that compensatory mechanisms were almost inoperative in BD, whereas a residual capacity to control peripheral resistance and cardiac contractility was present in AFB. Model simulations demonstrated that hypotension occurred later in AFB since the residual compensatory capacity in AFB was able to sustain the arterial pressure for larger BV reductions (8.3% BD vs. 11.2% AFB).

Conclusion. The increased risk of acute hypotension in BD compared to AFB is caused by a therapy-induced inhibition of reflex compensatory response to hypovolemia.

Key words: hypotension, bicarbonate dialysis, buffer-free dialysate, nitric oxide.

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Acute hypotension is a common intratreatment complication of chronic renal replacement therapies by hemodialysis, with an incidence still reported to be around the 20% to 30% of treatments [1, 2]. Apart from patient discomfort, acute hypotension also leads to a less effective treatment, especially in terms of body water removal. Sessions complicated by hypotension often end without achieving the correct dry body weight. In the long run, repetitive hypotensive episodes yield a chronic hydroelectrolytic derangement that promotes cardiovascular side-effects, leading the patient to have chronically unstable behavior.

Patient susceptibility to intradialytic hypotension exhibits large intrasubject variability and several factors have been ascribed to the pathogenesis of this complication. In subjects prone to acute hypotension, the first determinant of the hypotensive event is the hemodialysis-induced intravascular hypovolemia due to plasma-water ultrafiltration [2–4]. To prevent excessive hypovolemic stress, the online monitoring of circulatory blood volume reduction is rapidly gaining acceptance in clinical practice [5–7]. Actually, arterial pressure response is not simply determined by the blood volume changes since it closely depends on the short-term reflex capability to compensate for hypovolemia [8]. Indeed, significant differences between patients prone to hypotension can be noted also when the blood volume reduction is similar. Also, isovolemic hemodialysis can result in hypotension [9].

Additional therapy-related factors may potentially determine the patient's susceptibility to hemodialysis. Among these factors, the composition and quality of dialysate, filter membrane biocompatibility, and the convection/diffusion rate seem to influence the patient's tendency to acute hypotension. As a pertinent example, the replacement of most of the acetate with bicarbonate in standard hemodialysis has resulted in a decrease in intradialytic hypotensive episodes [10–12]. The role of acetate has been attributed to an acetate-induced impairment of cardiovascular reactivity. In fact, acetate dialysis stimulates nitric oxide synthesis [13] and endogenous nitric

oxide overload has a significant neuromodulator activity [14], with the net apparent effect of vagal activation and sympathetic inhibition [15]. Autonomic compensatory response plays a pivotal role in maintaining stable arterial pressure during hemodialysis. Thus, the patient's capacity to compensate for hypovolemia could be worsened by exposure to acetate as well as to other therapy-dependent stimuli because of the inhibition of the short-term autonomic-mediated reflex mechanisms controlling cardiovascular functions.

In line with this hypothesis, the present study investigated the cardiovascular compensatory response to hypovolemia, in a population of 12 end-stage renal disease (ESRD) hypotension-prone patients, during a widespread conventional therapy [bicarbonate dialysis (BD)]. In order to show that the dialysis technique directly impacts on the risk of hypotension, the same patients were also studied during an alternative technique [acetate-free biofiltration (AFB)], which has resulted in a better hemodynamic outcome [16]. A blood volume control system [17] was used in AFB to have blood volume changes similar to those observed in BD treatment. The effectiveness of the compensatory response to hypovolemia was then studied by means of model-based computer simulations of BD and AFB treatments.

METHODS

Subjects

Twelve patients with ESRD in renal replacement therapy with three times a week 4-hour maintenance double-needle hemodialysis at the dialysis center of the Infermi Hospital (Rimini, Italy) were enrolled ($N = 12$, four males and eight females; age 73.8 $\pm$ 8 years old, range 55 to 84 years; and weight 66 $\pm$ 11 kg, range 52.5 to 87.5 kg). All the participants provided informed consent for participation in this study.

Etiologies of the renal failure in the participants were nephrosclerosis (6), chronic glomerulonephritis (3), polycystic kidney disease (2), and diabetic nephropathy (1). No severe abnormalities were found upon physical examination. None of the patients had been treated with vasoactive substances, had experienced an acute myocardial infarction or chronic cardiac rhythm abnormalities nor had they been treated for heart failure. All the patients had a good vascular access (blood flow rate greater than 250 mL/min), an equilibrated Kt/V of at least 1.13, and residual diuresis lower than 400 mL/day.

All patients were classified as hypotension-prone based on recent incidence of hemodialysis-induced hypotension (at least two of their most recent 12 treatments complicated by acute hypotension). Intradialytic hypotension was defined as one of the following three situations: (*1*) systolic blood pressure $\leq$90 mm Hg, accompanied by symptoms and therapeutic maneuvers (saline or hypernatric infusions, plasma expander, Trendelenburg or other maneuvers, reduction in blood flow, stop of ultrafiltration); (*2*) systolic blood pressure reduction $\geq$25 mm Hg compared to the predialysis value, in the presence of symptoms and therapeutic maneuvers; or (*3*) systolic blood pressure $\leq$90 mm Hg, accompanied by a reduction of at least 20 mm Hg from the predialysis value. Incidence of hypotension was 2/12 in two subjects, 3/12 in one, 4/12 in two, 6/12 in two, 8/12 in two, 9/12 in one, and 10/12 in two.

Experimental design and run-in

After a run-in period, all the patients underwent a 4-week study period. The study was developed according to a prospective, crossover, parallel group design, with two sequences. Six patients were treated first with BD (2 weeks) and then by AFB (2 weeks) and six patients were treated first with AFB (2 weeks) and then by BD (2 weeks). One patient in the AFB-BD sequence dropped out because of a persistent intratreatment atrial fibrillation.

Each patient underwent an observational run-in period on conventional bicarbonate dialysis (see BD treatment, below) lasting 2 weeks. The run-in period was aimed at correcting and optimizing the prescription of postdialysis dry body weight and establishing the blood volume reduction to be set in the blood volume control system in the AFB treatment.

Postdialysis body weight was determined on the basis of both the traditional clinical parameters (skin and subcutaneous hydration state, jugular vein, predialysis and intradialytic blood pressure behavior, postdialysis standing blood pressure, and intratreatment symptoms, such as muscular cramps) as well as the radiologic signs related to the hydration status (cardiothoracic index, myocardial diameters, pulmonary blood flow distribution, and vascular pedicle aspect).

After having established the optimal dry body weight it was verified that postdialysis inferior vena cava diameter (VCD) determined by echography and corrected for body surface area was in the range of 10 to 14, which indicated an adequate cardiac filling pressure.

The weight loss normalized blood volume reduction (BV/WL) to be prescribed in the AFB treatment was established as the average of the spontaneous blood volume reductions at the end of the run-in sessions without hypotension, normalized with respect to the patient end-treatment weight loss.

BD treatment

The BD treatment was a conventional bicarbonate dialysis session [polysulphone (PS) membranes of 1.7 m^2 PS-low flux] (Fresenius MC AG, Bad Homburg, Germany). Dialysate flow rate was 500 mL/min and bath

temperature was constant at 36.5°C. Both the ultrafiltration rate and dialysate conductivity were kept constant during the treatment. The duration of dialysis was between 210 and 270 minutes. The composition of dialysate was sodium 140 mEql/L, potassium 2.5 mEq/L, bicarbonate 34 mEql/L, acetate 3.0 mEq/L, chloride 109 mEq/L, calcium 3.0 mEq/L, magnesium 1.0 mEq/L, and glucose 1.0 g/L. The percentage reduction of blood volume (%R-BV) was measured continuously during the entire treatment (Hemoscan™; Gambro-Dasco S.p.A., Medolla, Italy).

AFB treatment

The AFB treatment was acetate-free biofiltration with controlled blood volume. It consisted of a hemodiafiltration technique (polyacrylonitrile membrane AN69) (Hospal S.p.A, Bologna, Italy) in which the dialysate is buffer-free and acid-base correction is obtained by postfilter infusion of a 145 mEq/L sodium bicarbonate fluid [18]. The composition of dialysate was sodium 139 mEql/L, potassium 3.0 mEq/L, chloride 147.5 mEq/L, calcium 4.0 mEq/L, magnesium 1.0 mEq/L, and glucose 1.0 g/L. In order to deliver a blood volume reduction during the AFB treatment equivalent to the BD treatment a blood volume control system (Hemocontrol™) (Hospal S.p.A.) was employed. This automatic system continuously controls the blood volume profile during the session to obtain a goal blood volume reduction at the end of the treatment that is the prescribed BV/WL ratio. This is achieved by moment-to-moment adjustment of ultrafiltration rate and dialysate conductivity by a feedback control system using the deviation of measured %R-BV from the prescribed blood volume profile as input signal [17]. Other factors such as treatment time, blood and dialysate flow rates, and dialysate temperature were kept with the same as for the BD treatment.

Measurements and data collection

During each session (66 BD + 66 AFB), the %R-BV signal was acquired with a frequency of one sample per minute.

Systolic and diastolic arterial blood pressures were measured every 15 minutes by an automatic oscillometric sphygmomanometer (BP100) (Gambro AB, Lund, Sweden). The occurrence of typical low blood pressure symptoms (muscular cramps, headache, dizziness, vomiting, nausea, and sweating) and the times of any acute hypotension episodes were also recorded.

Since the model-based computer analysis was limited to the midweek dialyses only (two BD and two AFB for each patient), a 12-lead ECG Holter (H-12 Holter) (Mortara Instrument, Inc., Milwaukee, WI, USA) was recorded during these sessions and an array containing the beat-to-beat heart rate was extracted from the R-R time series. %R-BV and heart rate time series, before being analyzed by the model, were low pass filtered with a digital Butterworth filter to remove the high-frequency variability.

Plasma Na^+, K^+, Ca^{2+}, HCO_3^- concentrations, and pH were also measured before and after the midweek treatments (BG Electrolytes) (Instrumentation Laboratory, Milan, Italy).

Qualitative description of the computer model

Cardiovascular response to hemodialysis-induced hypovolemia was simulated using the mathematical model presented in previous works [8, 19] to which a few adjustments were made to analyze data from the present study. An accurate description of the mathematical model, including equations and parameter assignment, can be found on the Internet Web site *www-bio.deis.unibo.it/DialSim.html*. Here, only the main adjustments and the relevant improvements are outlined.

The model of the circulatory system was in accordance with the hydraulic equivalent already shown in [8]. Briefly, it includes (*1*) the systemic circulation comprised of three compartments in series (arterial, microcirculatory and venous); and (*2*) the cardiac pump represented by a single compartment (right atrium) and by the Starling law, linking the right atrium pressure to the stroke index.

The model of the short-term reflex compensation to hypovolemia was rearranged according to the block scheme shown in Figure 1. As in the previous formulation of the model, two distinct afferent pathways were considered: one for the arterial [20] and the other for the cardiopulmonary [21] sides. The model parameter, K_{aff}, allows the assignment of a different relative weight to the two pathways. Previous model-based analyses [8, 19] showed that in hypotension-prone patients K_{aff} typically ranges from -0.1 to -0.5, indicating that the afferent pathways are weighted toward the arterial side. K_{aff} was arbitrarily set to -0.3 for the analysis of data of present study's data.

Afferent pathways determine the efferent autonomic tone, in which accordance with current physiologic knowledge [22], drives the compensatory response to hypovolemia by way of four distinct mechanisms (see Fig. 1): (*1*) the decrease in venous capacity that causes an enhancement in the venous return; (*2*) the increase in total peripheral resistance that allows for the rise of arterial pressure in proximal arteries; (*3*) the increase in cardiac contractility; and (*4*) the increase in heart rate to optimize the cardiac output. Four distinct gains express the efficiency of the short-term reflex compensatory response: K_v for venous capacity, K_r for total peripheral resistance, K_{sv} for stroke volume, and K_{hr} for heart rate. Each of these parameters may range between 0 and 1. When the parameter is equal to 0, the corresponding

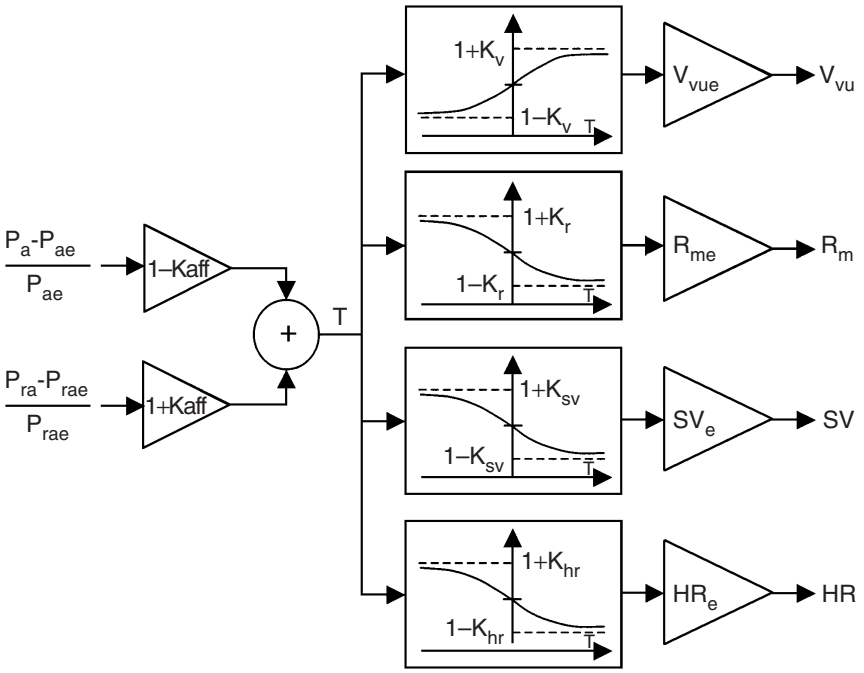

Fig. 1. Block diagram illustrating the model used to simulate the short-term compensatory mechanisms to hypovolemia. Variations of arterial (P_a) and right atrial (P_{ra}) pressures compared with the values at the beginning of treatment (P_{ae} and P_{rae}, respectively) excite the efferent adrenergic tone (T), which actuates vasoconstriction of both venous (V_{vu}) and microcirculatory (R_m) vessels, as well as improving cardiac function through inotropic regulation of stroke volume (SV) and chronotropic regulation of heart rate (HR). Adrenergic stimulation modifies the conditions of effectors relative to initial values (V_{vue}, R_{me}, SV_e, and HR_e). The effectiveness of each of these regulatory pathways was characterized by a parameter (K_v, K_r, K_{sv}, and K_{hr}) that can range from 0 to 1 (0 = total inhibition and 1 = maximal efficiency).

regulatory mechanism is inoperative, whereas the mechanism is maximally effective when the parameter is equal to 1.

In the previous model formulation, the measured heart rate was considered as a model input directly controlling the heart activity. Conversely, in the model used for the present analysis, the control of chronotropic and inotropic heart activity is operated through two negative compensatory feedbacks (the bottom two pathways in Fig. 1). This adjustment was introduced in order to have the heart rate as a model output quantity to be compared with the measured one.

A relevant improvement concerns the computation by the model of both diastolic and systolic blood pressure, since both these quantities were available as measured data. A simple Windkessel equation [23], based on the total peripheral resistance and arterial compartment compliance, was used to calculate the typical systolic rise and diastolic drop in arterial pressure in the course of the cardiac cycle by imposing the cardiac output computed by the model. The maximum and minimum of this pressure curve were considered as the systolic (P_s) and diastolic (P_d) pressure, respectively. The mean arterial pressure, derived according to the formula $P_m = 2/3 * P_d + 1/3 * P_s$, was then used in the circulatory model as in the previous implementation.

The identification process reflects all the modifications made to the model structure. In regard to the previous formulation, only the %R-BV was used as model input while systolic and diastolic arterial pressure as well as heart rate simulated by the model (i.e., the model outputs) were used in the identification process of the control loop model parameters.

Data analysis by computer model

%R-BV data collected in each study session was imposed as time-varying input to the computer model and model equations were numerically solved in order to compute the simulated systolic and diastolic arterial pressures as well as the simulated heart rate as a function of dialysis time. In the case of sessions with hypotension, simulation was limited to 15 minutes before the hypotension onset since following data could be confounded by the therapeutic maneuvers employed (e.g., infusion, reduction in blood flow, cessation of ultrafiltration).

By using an iterative procedure, the optimal values of the model parameters K_v, K_r, and K_{sv} were identified by best-fitting simulated pressure and heart rate curves to the measured data. The parameter K_{hr} was not included in the identification procedure and a fixed value was used ($K_{hr} = 0.4$). After parameter identification, the changes in stroke volume, cardiac output, total peripheral resistance and venous capacity occurring in each study session were estimated. The accuracy of the model in predicting such hemodynamic quantities has been examined in a previous study [8].

Statistical analysis

The results are expressed using mean ± SD. For the model parameters 25th and 75th percentiles are also reported. Frequency of hypotension episodes and symptoms in the two dialysis techniques were compared through paired *t* test. Collapse time and %R-BV in the two techniques were compared through unpaired two sample *t* test. Repeated measures analysis of variance (ANOVA) was used to perform a factorial analysis

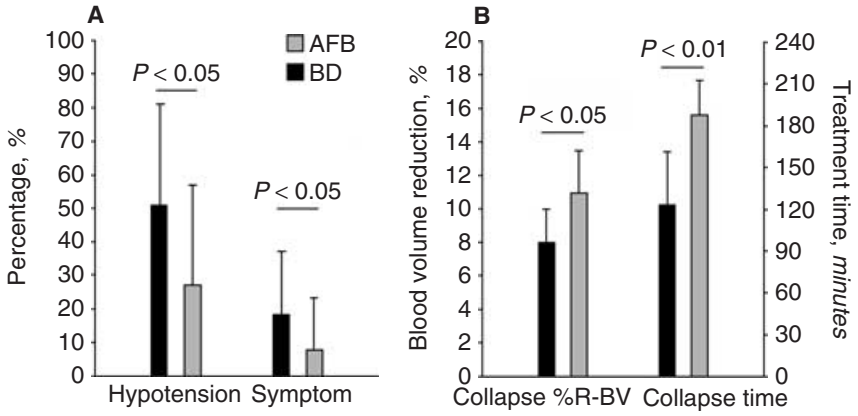

Fig. 2. Comparison of hypotensive episodes and collapse. (*A*) Frequency of dialyses complicated by hypotensive episodes [hypotension 51% ± 30% for bicarbonate dialysis (BD) vs. 27% ± 30% for acetate-free biofiltration (AFB)] and by at least one symptom (symptoms 18% ± 19% for BD vs. 7% ± 15% for AFB). Frequencies were calculated for each patient as the incidence of sessions with complications over the six BD and six AFB sessions, respectively; mean ± standard deviation of these frequencies for the 11 patients are shown. (*B*) Percentage reduction in blood volume before the hypotension episode [collapse percentage reduction of blood volume (%R-BV) 7.9% ± 2.0%, $N = 34$ for BD vs. 10.9% ± 2.6%, $N = 18$ for AFB) and time of hypotension (collapse time 123 ± 41 minutes for BD vs. 183 ± 25 minutes for AFB).

Table 1. Incidence of sessions complicated by acute hypotension during the 4 weeks of study

	Hypotension Incidence			
	First 2 weeks		Second 2 weeks	
Sequence	BD	AFB	AFB	BD
BD-AFB	17/36 (57%)		7/36 (23%)	
AFB-BD		11/30 (31%)		17/30 (47%)

Abbreviations are: BD, bicarbonate dialysis; AFB, acetate-free biofiltration.

and to test the dependence of each quantity on two intrasubject parameters: time during dialysis and dialysis technique. Differences were considered as statistically significant when the box-corrected probability level on the within-subject F tests was less than 0.05. Arterial pressure and heart rate predicted by the computer model were compared with measured values, according to the Bland-Altman method [24].

RESULTS

Hypotension

The incidence of sessions complicated by hypotensive episodes was almost double in BD compared to AFB (34/66 for BD vs. 18/66 for AFB). One patient had more hypotensive episodes in AFB (4/6 for BD vs. 5/6 for AFB), while the other 10 subjects developed symptomatic hypotension more frequently during BD treatments (50% ± 29% for BD vs. 15% ± 19% for AFB). Also sessions without acute hypotension, but with patient discomfort, were more frequent in BD than in AFB (Fig. 2A). The larger incidence of hypotension in BD treatment was observed independently of the order in which the two treatments were delivered (Table 1).

Importantly, the critical blood volume reduction (i.e., the %R-BV at which collapse occurred) was lower in BD than in the AFB (Fig. 2B). Similarly, hypotensive episodes occurred around 60 minutes sooner in BD than in AFB (Fig. 2B). No differences were noted in the total weight loss between the two treatments (2.28 ± 0.61 kg for BD vs. 2.24 ± 0.75 kg for AFB).

The hypotension outcome clearly indicated that the BD treatment increases the risk of acute intradialytic hypotension by reducing patient's resistance to hypovolemia. To assess whether this phenomenon was due to differences in the effectiveness of the compensatory response to hypovolemia we used model-based computer analysis.

Validation of computer model predictions

After model parameter identification, the arterial pressure and heart rate predicted by the model were compared with measured values (see Fig. 3). The comparison evidenced a good correlation as confirmed by the high R coefficient values for systolic pressure (0.93, $P < 0.001$), for diastolic pressure (0.91, $P < 0.001$), and for heart rate (0.89, $P < 0.001$). Of the differences in systolic pressure, 69.5% were within ±6.5 (±SD) mm Hg, 71.5% of the differences in diastolic pressure were within ±6.4 (±SD) mm Hg, and 60.5% of the differences in heart rate were within ±4.5 (±SD) bpm. The mean error was determined as 0.5% ± 3.7% for systolic pressure, 0.6% ± 4.4% for diastolic pressure, and 1.6% ± 4.1% for heart rate. These results confirmed the model's reliability in predicting the measured data.

Results of model analysis of the sessions not complicated by hypotension are presented set apart from results obtained in sessions with hypotension, in order to distinguish between the different dialysis outcomes.

Model-based analysis of hypotension-free sessions

Eight patients were included in this analysis: four patients with all the midweek sessions (two BD and two AFB) hypotension-free and the other four patients for whom only two sessions (one BD and one AFB) were

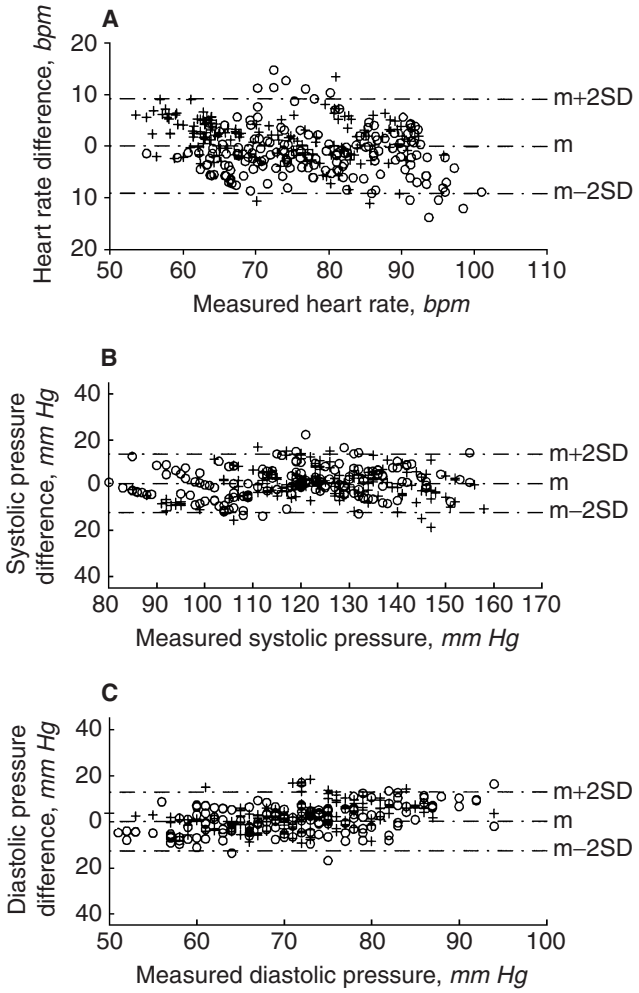

Fig. 3. Bland-Altman scatter plot of differences between simulated and measured heart rate (*A*), systolic pressure (*B*), and diastolic pressure (*C*) for bicarbonate dialysis (BD) (○) and acetate-free biofiltration (AFB) (+). Mean values ± standard deviations of the differences were: 0.01 ± 4.59 bpm for heart rate, 0.74 ± 6.46 mm Hg for systolic pressure, and −0.05 ± 6.38 mm Hg for diastolic pressure.

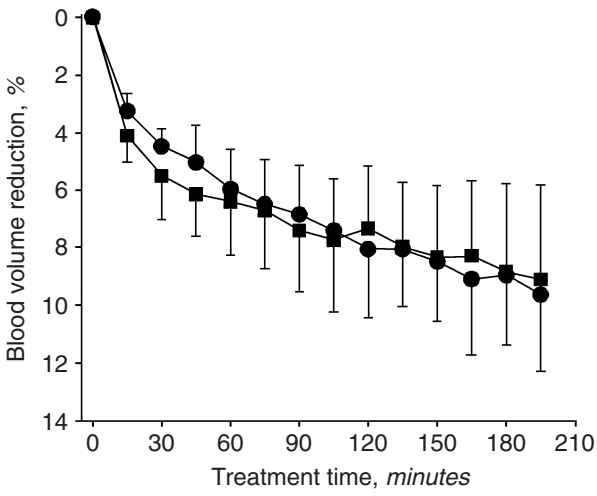

Fig. 4. Percentage reduction in blood volume in 12 bicarbonate dialysis (BD) (●) and in 12 acetate-free biofiltration (AFB) (■) sessions without hypotension. No significant difference was found between the two treatments (see Table 3).

Table 2. Electrolytes concentrations and pH in sessions without hypotension [12 bicarbonate dialysis (BD) vs. 12 acetate-free biofiltration (AFB)]

Chemical	Treatment	Sample Time		ANOVA Treatment
		Pre	Post	
Na^+ *mEq/L*	BD	139.2 ± 1.9	138.7 ± 1.5	NS
	AFB	138.8 ± 1.5	138.9 ± 2.1	
Ca^{++} *mEq/L*	BD	1.08 ± 0.14	1.13 ± 0.14	NS
	AFB	1.13 ± 0.09	1.18 ± 0.18	
K^+ *mEq/L*	BD	5.11 ± 0.53	3.94 ± 0.28	NS
	AFB	5.09 ± 0.39	3.86 ± 0.31	
HCO_3^- *mEq/L*	BD	23.13 ± 2.03	27.74 ± 2.55	NS
	AFB	23.56 ± 1.71	27.75 ± 2.31	
pH	BD	7.36 ± 0.03	7.46 ± 0.04	NS
	AFB	7.37 ± 0.02	7.45 ± 0.03	

Abbreviations are: ANOVA, analysis of variance; Pre, values measured before haemodialysis; Post, values measured at the end of the hemodialysis; NS, not significant.

hypotension-free. The remaining three patients were not included since both the midweek BD sessions were complicated by hypotension. Notably, these three patients showed the highest hypotension frequency (5/6 in BD treatment). Altogether, 12 BD and 12 AFB hypotension-free sessions were considered.

According to the experimental design, the use of the blood volume control system allowed the AFB treatments to be delivered with blood volume reductions similar to those observed in BD (Fig. 4). The electrolyte plasma concentrations and pH also exhibited similar changes (Table 2).

Systolic and diastolic pressures tend to remain stable throughout both treatments. A slightly lower systolic pressure in the BD was observed (Table 3). Conversely, a notable difference was evident in the heart rate, which rises significantly in BD, whereas it remains stable in the AFB treatment (Table 3).

Analysis of model parameters in the hypotension-free sessions (Table 4) revealed that cardiovascular reactivity was worse in the BD treatments than in the AFB treatments. In fact, all the parameters were on average lower in the BD therapy than in AFB. The difference was especially significant in the parameter K_r related to the control of microvascular resistance and in the parameter K_{sv} expressing the efficacy of inotropic control of cardiac contractility.

Differences in the effectiveness of compensation to hypovolemia were also evident: the increase in total peripheral resistance in AFB was twice that exhibited in BD; whereas, the decrease in stroke volume was twice greater in BD compared to AFB (Table 5).

Table 3. Pressure, heart rate, and blood volume in sessions without hypotension [12 bicarbonate dialysis (BD) vs. 12 acetate-free biofiltration (AFB)]

		Treatment time *minutes*			ANOVA	
		0	90	180	Time	Treatment
Systolic pressure *mm Hg*	BD	122.4 ± 14.1	114.5 ± 16.4	114.8 ± 18.4	NS	$P < 0.01$
	AFB	120.1 ± 12.4	123.4 ± 17.8	122.6 ± 12.1		
Diastolic pressure *mm Hg*	BD	72.1 ± 10.1	68.7 ± 10.5	69.7 ± 11.9	NS	NS
	AFB	66.4 ± 5.9	71.7 ± 8.9	72.9 ± 11.4		
Heart rate *bpm*	BD	69.7 ± 9.73	78.7 ± 9.7	83.3 ± 9.5	$P < 0.05$	$P < 0.01$
	AFB	71.5 ± 9.8	71.8 ± 12.3	75.2 ± 11.1		
Blood volume reduction %	BD	–	6.84 ± 1.71	8.95 ± 2.41	$P < 0.01$	NS
	AFB	–	7.41 ± 2.12	8.81 ± 3.05		

ANOVA is analysis of variance and NS is not significant.

Table 4. Model parameter identification in sessions without hypotension

	BD ($N = 12$)	AFB ($N = 12$)	*t* test
K_v mean ± SD	0.35 ± 0.25	0.60 ± 0.23	NS
(25% to 75%)	(0.10–0.41)	(0.30–0.91)	
K_r mean ± SD	0.24 ± 0.24	0.90 ± 0.15	$P < 0.001$
(25% to 75%)	(0.10–0.42)	(0.70–0.94)	
K_{sv} mean ± SD	0.21 ± 0.3	0.73 ± 0.4	$P < 0.01$
(25% to 75%)	(0.10–0.4)	(0.30–0.92)	

Abbreviations are: BD, bicarbonate dialysis; AFB, acetate-free biofiltration; K_v, efficiency of venous capacity regulation (maximum efficiency $K_v = 1$); K_r, efficiency of peripheral resistance regulation (maximum efficiency $K_r = 1$); K_{sv}, efficiency of stroke volume regulation (maximum efficiency $K_{sv} = 1$); NS, not significant.

Table 5. Percent changes of cardiac output (CO), total peripheral resistance (TPR), stroke volume (SV), and venous capacity (VC) in sessions without hypotension

	BD ($N = 12$)	AFB ($N = 12$)	*t* test
ΔCO %	−2.1 ± 6.3	−3.1 ± 5.1	NS
ΔSV %	−19.1 ± 8.2	−10.7 ± 7.8	$P < 0.01$
ΔTPR %	9.1 ± 9.4	18.9 ± 6.6	$P < 0.05$
ΔVC %	−14.7 ± 5.5	−14.8 ± 4.5	NS

Abbreviations are: BD, bicarbonate dialysis; AFB, acetate-free biofiltration; ΔCO, percent changes in cardiac output; ΔTPR, percent changes in total peripheral resistance; ΔSV, percent changes in stroke volume; ΔVC, percent changes in venous capacity; NS, not significant.

The mean values of the K_v, K_r, and K_{sv} parameters were considered to be representative of the compensatory response exhibited in the BD and AFB treatments without hypotension. Using these two sets of mean parameters (see Table 4) and the blood volume curves shown in Figure 4 as model input, virtual BD and AFB treatments were simulated. The systolic and diastolic arterial pressures as well as the heart rate of the virtual treatments were then compared with the corresponding experimental data (see Fig. 5) to demonstrate that the two sets of parameters characterize the mean response in BD and AFB during hypotension-free sessions.

A comparison between the cardiovascular responses predicted by the model for the virtual BD and AFB sessions is shown in Figure 6. Cardiac output as well as venous pressure appear to follow the same trend in both treatments. On the other hand, treatment differences are clearly evident for peripheral resistance and stroke volume. The latter fell markedly in the BD treatment (−23% at 180 minutes), whereas the reduction was moderate in the AFB treatment (−10% at 180 minutes).

Model-based analysis of sessions with hypotension

Seven patients were included in the analysis of sessions with hypotension: four patients with only one BD and one AFB sessions complicated by hypotension and three patients experiencing hypotension in both the midweek BD sessions. For this second group of patients, one had both the AFB sessions complicated by hypotension, whereas the other two patients had only one midweek AFB session with hypotension. For these two patients, just one of the two BD sessions was considered, in order to maintain a balanced data set. Thus, eight BD and eight AFB sessions with hypotension were considered.

In both BD and AFB treatments, the parameter K_v was close to zero (Table 6), suggesting that the adaptation of venous capacity to hypovolemia was ineffective in the sessions with hypotension. Both K_r and K_{sv} were close to zero in the BD treatments, whereas these parameters were significantly higher in the AFB treatments (see Table 6).

To compare the pressure response to hypovolemia in two treatments, the mean values of the BD and AFB parameters (Table 6) were used to simulate BD and AFB dialyses with a linearly decreasing blood volume that resulted in a 15% reduction in the blood volume after 4 hours. The results of these simulations are shown in Figure 7, where the systolic pressure is plotted as a function of the blood volume reduction. In BD, the complete lack of effectiveness in compensation ($K_v = 0.02$, $K_r = 0.05$, $K_{sv} = 0.05$) causes the systolic pressure to fall swiftly in response to hypovolemia. Under this condition, the hypotension threshold is reached at a blood volume reduction of about 8%. Notably, this value closely matches the critical blood volume observed in the BD sessions with

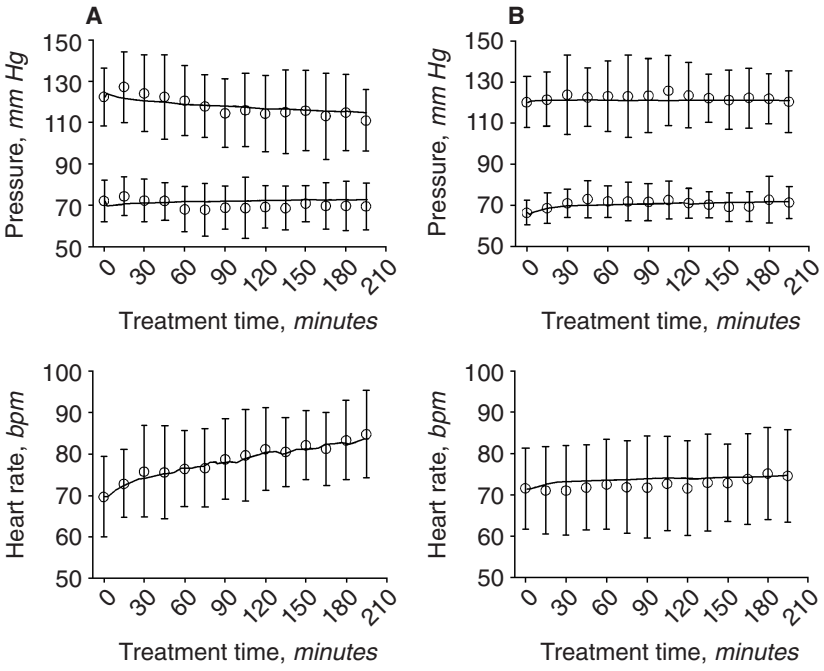

Fig. 5. Comparison of simulated and measured arterial pressure and heart rate (mean ± SD) in bicarbonate dialysis (BD) (*A*) and acetate-free biofiltration (AFB) (*B*) sessions without hypotension. Model simulated pressure and heart rate (continuous lines) used the percentage reduction of blood volume (%R-BV) curves shown in Fig. 4. as input. For the simulation, the mean values of parameters identified in the hypotension-free sessions (see Table 4) were assigned (BD $K_v = 0.35$, $K_r = 0.24$, and $K_{sv} = 0.21$; AFB $K_v = 0.60$, $K_r = 0.90$, $K_{sv} = 0.73$).

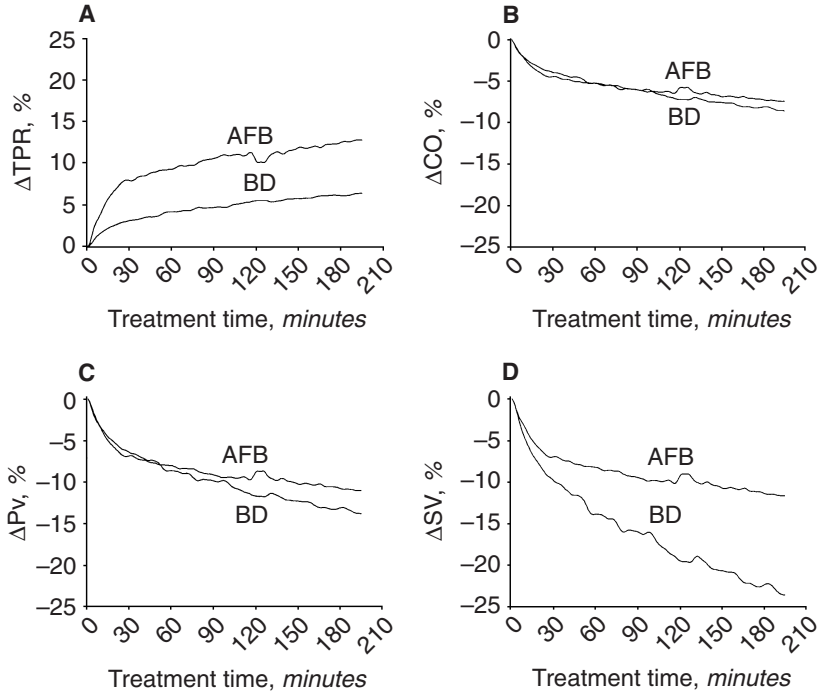

Fig. 6. Percentage changes in total peripheral resistance (TPR) (*A*), cardiac output (CO) (*B*), venous pressure (P_v) (*C*), and stroke volume (SV) (*D*) simulated by the model during bicarbonate dialysis (BD) and acetate-free biofiltration (AFB) without hypotension. The percentage reduction of blood volume (%R-BV) curves used as model inputs are shown in Fig. 4. Parameters are those reported in Fig. 5. Peripheral resistance and stroke volume exhibited notable differences.

hypotension (see Fig. 7). In the case of AFB treatment, the residual control of vascular resistance and heart contractility ($K_v = 0.01$, $K_r = 0.49$, $K_{sv} = 0.50$) maintains a sustained pressure up to a 5% blood volume reduction. Beyond this value, pressure falls and the hypotensive threshold is crossed at a blood volume reduction of about 12%. This value also closely agrees with the critical blood volume threshold observed in AFB with hypotension (see Fig. 7). Hypotension occurs about 60 minutes earlier in BD than AFB (see Fig. 7) that is comparable to the timing of hypotension observed in the experimental results.

DISCUSSION

In this study we have examined the impact of the technique used to deliver hemodialysis treatment on the cardiovascular system, focusing on the risk of hypotension in hypotension-prone patients. For this purpose,

Table 6. Model parameter identification in sessions with hypotension

	BD ($N = 8$)	AFB ($N = 8$)	t test
K_v mean ± SD	0.02 ± 0.07	0.01 ± 0.03	NS
(25% to 75%)	(0.00–0.07)	(0.00–0.05)	
K_r mean ± SD	0.05 ± 0.09	0.49 ± 0.16	$P < 0.01$
(25% to 75%)	(0.00–0.07)	(0.39–0.52)	
K_{sv} mean ± SD	0.05 ± 0.09	0.50 ± 0.27	$P < 0.01$
(25% to 75%)	(0.00–0.05)	(0.44–0.53)	

Abbreviations are: BD, bicarbonate dialysis; AFB, acetate-free biofiltration; K_v, efficiency in the venous capacity regulation (maximum efficiency $K_v = 1$); K_r, efficiency in the peripheral resistance regulation (maximum efficiency $K_r = 1$); K_{sv}, efficiency in stroke volume regulation (maximum efficiency $K_{sv} = 1$); NS, not significant.

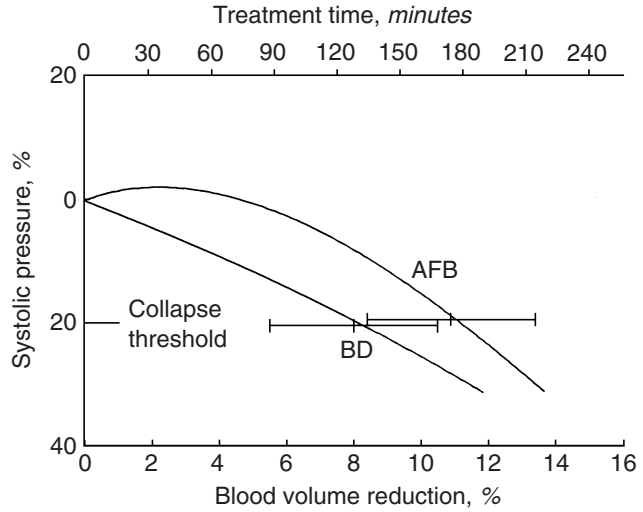

Fig. 7. Percentage change of systolic pressure simulated by the model during a treatment that produces a percentage blood volume reduction of 15% after 4 hours. The parameter values used for the simulations are the mean values identified in hypotensive sessions [bicarbonate dialysis (BD) $K_v = 0.02$, $K_r = 0.05$, $K_{sv} = 0.05$; acetate-free biofiltration (AFB) $K_v = 0.01$, $K_r = 0.49$, $K_{sv} = 0.50$]. The critical percentage reduction of blood volume (%R-BV) for the occurrence of hypotensive episodes in BD and AFB treatments are also shown (mean ± SD).

the hemodynamic response to conventional dialysis using a predominantly bicarbonate-based buffer with a small amount of acetate (BD), the worldwide dominant hemodialysis modality, was compared with the hemodynamic response to AFB, a technique that uses a buffer-free dialysate with continuous post-filter infusion of a sterile bicarbonate solution [25]. BD was proposed to improve the hemodynamic stability compared with acetate dialysis [11, 26, 27]. However, this benefit has not always been confirmed [28, 29] and the improvement of dialysis morbidity with BD remains controversial. AFB has been proposed as an alternative to acetate or bicarbonate hemodialysis that gives better cardiovascular stability [30, 31]. In a crossover study Zucchelli, Santoro, and Spongano [16], showed that the percentage of sessions with symptomatic side-effects was lower in AFB than in BD and that hypotensive events decreased significantly. Hypotension incidence as well as symptomatic side-effects observed in the present study (see Fig. 2) attested to such differences. With respect to previous studies, we assured each patient had a similar blood volume reduction and dry body weight in both treatments. Thus, we can exclude that different hypotensive risk associated with BD and AFB was due to a different therapy-induced hypovolemia or body weight loss.

A novel result was that the critical blood volume threshold (i.e., the relative blood volume reduction at which acute hypotension occurred) was significantly lower in BD than in AFB (7.9% ± 2.0% BD vs. 10.9% ± 2.6% AFB). As a direct consequence, hypotensive events also occurred earlier in BD, thus demonstrating a different cardiovascular tolerance to blood volume withdrawal between BD and AFB.

Differences between the two treatments were also evident when only the sessions uncomplicated by hypotension were considered. In hypotension-free BD sessions, systolic pressure was lower at the end of treatment compared to AFB sessions whereas heart rate was higher (see Table 3). To our knowledge, previous comparisons of hemodynamic response between different dialysis techniques did not distinguish between sessions with and without hypotension. Acute hypotension is associated with large reactive hemodynamic changes. Therefore, we considered it appropriate to study the actual impact of therapy on the cardiovascular system in hypotension-free sessions where confounding reactive factors did not influence the hemodynamics. Since treatment differences were evident also in hypotension-free sessions, we advanced the hypothesis that BD systematically reduces the cardiovascular compensatory responsiveness to hemodialysis-induced hypovolemia.

To explore this hypothesis we utilized a model-based computer analysis successfully used in the past to study the role of compensatory mechanisms on the pressure response to hypovolemia [8]. The model-based approach constituted a quantitative framework useful for giving a coherent explanation of the experimental observations. A significant model improvement was the computation of both systolic and diastolic arterial pressure. Apart from the advantage of having twice the number of points available for the identification procedure, the tuning of model parameters improved since systolic and diastolic pressure reflect different information. Systolic pressure depends more on cardiac output which is determined by myocardial contractility and heart frequency, whereas diastolic pressure is mainly influenced by the total peripheral resistance which depends on the smooth muscle tone of small arteries and arterioles.

In the present investigation, model analysis was crucial in providing an explanation of the different heart rate response observed in BD compared with AFB (Table 3). The presence of a small amount of acetate in the BD dialysate may be significant. Vincent et al [32] observed

a myocardial depression induced by acetate buffer with a significant increase in the heart rate. However, a direct tachycardic effect of acetate upon the sinus node can be excluded since a decrease in the heart rate generally follows acetate administration in animals [33].

To test the hypothesis that the different heart rate response reflected the difference in arterial pressure only and was not due to a direct effect of the therapies upon the sinus node, we assigned a fixed value to the model parameter K_{hr}. The good agreement between the heart rate simulated by model and measured heart rate (see Fig. 5) validated this assumption. Under this condition, model-based analysis revealed the important findings that peripheral resistance constriction as well as cardiac inotropism were blunted in hypotension-free BD sessions. As a direct consequence, in the BD treatment, chronotropic activation raised the heart rate in order to maintain adequate cardiac output in the presence of blunted inotropic control. In AFB, on the other hand, vasomotor and cardiac contractility compensation was able to sustain pressure without activating the baroreflex increase in heart rate. Therefore, the increased heart rate during BD may be ascribed to a positive compensation for a therapy-induced depression in the contractile force of vascular smooth muscle and cardiac fibers.

Model-based analysis also revealed the ineffectiveness of venous compensation in dialysis sessions complicated by hypotension (K_v close to 0 in both BD and AFB techniques). On the contrary, in the hypotension-free sessions the venous capacity control was adequate in assuring hypovolemia compensation ($K_v = 0.35 \pm 0.25$ in BD and $K_v = 0.60 \pm 0.23$ in AFB). The pivotal role of venous capacity in the genesis of hypotension was confirmed by the inverse relationship between the K_v values and the tendency to intradialytic hypotension: the three patients with the highest frequency of hypotension (78% of BD treatments) had $K_v = 0$, whereas the three patients with the lowest incidence of hypotension (less than 30% of BD treatments) had the highest K_v values ($K_v > 0.4$).

An equivalent discriminating role was not evident with regard to peripheral resistance. In fact, in the sessions complicated by hypotension the compensation of peripheral resistance and stroke volume was again operative in AFB, whereas it was ineffective in BD (see Table 6). The unique difference ascribable to peripheral resistance was the time of acute hypotension (see Fig. 7), which was about 60 minutes earlier in BD than in AFB. Previous investigations [34, 35] pointed out the inability to distinguish patients with a stable or unstable pressure response to dialysis on the basis of peripheral vascular resistance alone. According to our observations, the effectiveness of venous capacity adaptation may be the crucial element for cardiovascular stability during hemodialysis-induced hypovolemia.

Evidence of venous pooling or impaired venous tone in hemodialysis-induced hypotension in the presence of blood volume reduction has already been reported [8, 36]. Dialysis patients with diastolic dysfunction due to high sensitivity to cardiac filling pressure particularly suffer from impaired venous capacity control [37]. Venous tone affects cardiac filling during blood volume withdrawal. The more venous capacity is reduced, the less venous return is assured to the right heart and thus indirectly the cardiac output drops. Furthermore, effective regulation of arterial vascular resistance coupled with inadequate control of venous capacitance may trigger a dangerous positive feedback. Blood volume withdrawal induces an uncompensated lowering of venous pressure with a consequent reduction in cardiac output responsible for a decrease in arterial pressure that stimulates peripheral vasoconstriction, which by closing the unstable loop causes a further decrease in venous pressure. This behavior was evident in the simulation of AFB with hypotension, where in the initial phase of hypovolemia, thanks to the increase in arterial peripheral vascular resistance, a paradoxic increase in the arterial pressure was evident (see Fig. 7). However, in the second phase, the blood pressure dropped sharply even if the control of peripheral resistance was operative because of the absence of venous capacity compensation.

Notably, the present study has demonstrated a therapy-induced deficiency in vessel and cardiac contractility in BD treatment. Since a primary autonomic dysfunction can be excluded, the reduced cardiovascular responsiveness in the BD treatment can be associated to an apparent inhibition of α- and β-adrenergic stimulation. However, the heart rate increase in BD is indicative of adequate cardiac sympathetic tone. Therefore, the blunted contraction of vascular smooth muscle and cardiac fibers during BD could reflect the inhibition of intracellular effectors for the action of adrenergic receptor stimulation.

One possible explanation for the reduced responsiveness to adrenergic stimulus could be an enhanced production of endogenous nitric oxide in BD compared to AFB, since nitric oxide overload inhibits the contractile responses to adrenergic stimulation by limiting the transmembrane calcium L-type current [38]. The hypothesis that an enhanced production of nitric oxide causes the inhibition of sympathetic activity in patients with acute hypotensive episodes has already been advanced [39]. Beasley and Brenner [40] investigated the role of nitric oxide in hemodialysis hypotension and proposed the hypothesis that hypotension is mediated by inflammatory cytokine-induced NO production in vascular smooth muscle cells. Acetate-containing dialysate [41] or filter membrane [42, 43] is likely to stimulate the production of the cytokine activators of nitric oxide synthesis. AFB has been shown to cause less monocyte activation and cytokine release than BD [44]. Moreover, in vitro studies

on the effects of dialysate solutions with and without acetate on the nitric oxide synthase (NOS) activity found that acetate-containing dialysate up-regulated nitric oxide production in endothelial cells [13, 45]. Emerging evidence indicates that the responsiveness of the endothelium to hemodialysis therapy may play a key role in hemodynamic instability due to endothelium-derived nitric oxide and endothelin [46]. Hence, the hypothesis could be advanced that BD treatment causes a deficient cardiovascular responsiveness in hypotension-prone patients because of an enhanced stimulation of nitric oxide production in vascular smooth muscle and cardiac fibers.

An alternative or complementary plausible cause for the enhanced adrenergic responsiveness in AFB could be associated with the post-filter infusion of bicarbonate buffer and with the significant convective mass transfer that results. Purely convective transport across the dialysis membrane has long been known to promote better cardiovascular stability [47]. Moreover, in AFB the subject receives direct infusion of bicarbonate solution that is at room temperature. Infusion of cold fluid could have an impact on the cardiac and vascular reactivity comparable to cooled conventional dialysate, which has generally been associated with increased cardiovascular stability [48]. Thus, the disparity in the cardiovascular reactivity between conventional BD and AFB could be also ascribed to differing thermal balance and/or differing vasoactive middle molecule removal because of the different levels of convection present in the two therapies.

CONCLUSION

In the hypotension-prone patient, conventional BD increases the risk of hypotension compared to AFB since it worsens the patient's responsiveness to hypovolemia. Model-based computer analysis has revealed a therapy-specific worsening of cardiovascular compensatory response to adrenergic stimulation during BD treatment.

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